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Commentary: Mapping Early Symptom Trajectories in Autism Spectrum Disorder: Lessons and Challenges for Clinical Practice and Science

Variability in the trajectory of clinical symptoms in the early emerging presentation of young children with autism spectrum disorder (ASD) exists both within an individual child over time and between different children at any point in time and also across time. Georgiades and colleagues[1] recently coined the term 'chronogeneity' to indicate these within- and between-participant patterns of variability over time. In clinical practice this is often the focus of questions that parents ask clinicians at or soon after diagnosis: "Can you tell us what the future holds and will his (her) symptoms improve or get worse?". The variability or heterogeneity within and between children on the autism spectrum makes that a tough question to answer; however well one understands the motivation of the parent/carer in asking it.

One study design that helps us understand these patterns of heterogeneity are naturalistic, longitudinal observational studies. The authors[2] [**Note to Editorial Office: I do not know the authors of the article**] of the current article use such a design but go beyond previous studies (including their own) by reporting on multiple repeated sampling using the Autism Diagnostic Observational Schedule (ADOS) in very young children with emerging ASD. The repeat sampling was intensive (involving a total of 912 observations on a sample of 149 children with a mean of 6 ADOS administrations at 2.5 month intervals) and across a very young age span (from 14 to 36 months of age). The authors also extended previous work by reporting on the ADOS calibrated severity score which allows direct comparison across different Modules of the instrument (chosen based on the child's age and language ability) and are more immune from the effects of age and cognitive ability. They also report on individual symptom trajectories derived from ADOS items.

They use a latent class growth analysis statistical method (Proc Traj) that identifies sub-populations of individuals with different growth trajectories.

Four clusters (or classes) were identified, each comprising approximately one quarter of the sample: Non-spectrum (25%), Worsening (27%), Moderately-improving (25%) and Severe-persistent (23%). As would be expected, the clusters varied in their ASD severity, adaptive functioning and verbal and non-verbal developmental abilities at both baseline and final evaluations, as well as the proportion who received an ASD diagnosis at the outcome evaluation. The Non-spectrum group contained few children with a final diagnosis of ASD, around a third with other developmental delays and 60% of children with typical development. They had higher baseline and final developmental and adaptive abilities. The Severe-persistent group all had a final diagnosis of ASD and the lowest developmental and adaptive abilities at both baseline and the final evaluation.

In many ways the most intriguing groups are those with patterns of worsening or improving ASD symptoms over time. The Worsening group had average non-verbal ability (NVIQ = 101) but considerably lower verbal ability (VIQ = 75) at baseline and both were higher than in the Moderately-improving and Severe-persistent groups. This is similar to the pattern reported in children with a later onset or emergence of ASD symptoms seen in familial high-risk sibling studies, both across a similar early preschool timeframe as in the present study[3] and in those who receive an ASD diagnosis in mid-childhood but did not when assessed at age 3 years[4,5,6]. One notable feature of the Worsening group was that despite having increasing ASD symptoms they showed considerable improvements in language and communication skills and adaptive abilities over time. This suggests a de-coupling between ASD symptom severity and developmental and adaptive skills, as has previously been reported for children with ASD followed from 3 to 6 years of age[7]. Another feature of the pattern of change over time in the Worsening group was that at the individual item level there were notable increases (or rather the emergence) in several items in the restricted and repetitive behaviours domain such as intonation, stereotyped language and restricted

interests but stability and even improvements in items in the social affect domain such as overall level of language and response to joint attention. This has been reported previously in children followed from 2 to 7 years[8] and may indicate that some patterns of rigid and repetitive behaviours might not be evident in young children with ASD until their language and cognitive capacity (e.g. to have intense interests or unusual intonation) are sufficiently developed. However, it might also indicate that at very young ages we should be looking for different, earlier emerging, aspects of rigid and restricted patterns of behaviour in observational assessments such as the ADOS and the companion parental interview the ADI-R.

The Moderately-improving group also showed differences in their trajectories of social affect and repetitive and restricted behaviour symptoms over time; with improvements in the former but stability in the latter. Even within the social affect domain at the individual item level this group showed improvement in some (e.g. response to name, amount of social overtures) but not all areas (e.g. poor shared enjoyment, integration of gaze with other modes of communication). However, it was not the case that children in the Moderately-improving group were 'growing out of their autism' as all but one child had an ASD diagnosis at the final evaluation. Rather it indicates that some of their social communication impairments ameliorated over time: one quarter had acquired functional phrase speech by 3 years and their adaptive skills modestly improved.

What this study highlights is not just the presence of different trajectories early in ASD development but how within each cluster there exist differences within and across the social affect and repetitive and restricted behaviours domains of symptoms measured by the ADOS, as well as language, non-verbal and adaptive skills. This variation in symptom trajectories and developmental abilities does not all move in the same direction. That is, individual clusters and individual children within clusters can have distinct trajectories – the 'chronogeneity' described above[1]. The authors outline the implications of their findings for ongoing monitoring and assessment of at-risk or referred toddlers, as well as the need for intervention field to adopt a sophisticated approach to design trials to account for this naturalistic variation between and within children with ASD over

time. Another area of clinical science that can learn from the rich 'natural histories' described by the authors is the arena of identifying biomarkers and the adoption of precision medicines approaches to understanding the underlying mechanisms that lead to atypical development in ASD and variation over time. The call for such approaches is not new[9] but the recognition that biomarker discovery science is not aiming for a static target (as in the traditional case-control design with groups of patients and non-patients) but a rich and complex moving target (or rather targets) presents considerable challenges to the field. It reassures clinical scientists involved in longitudinal cohort studies (or at least this one) that despite the fact that they can be viewed as rather simple or even old-fashioned in design they yield vital information about the natural course of neurodevelopmental conditions such as ASD that need to inform and underpin future treatment and translational research.

[Word count = 1,170]

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